TECHNICAL COMMENTARY

MRI

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Introduction

The technology of structural magnetic resonance imaging (MRI) is based on the magnetisation properties of cellular protons. The application of a strong magnetic field causes the protons within cells to shift direction, which will return to their original position over time ("precession"). The rate of precession differs across tissue types (such as grey matter and white matter in the brain), which can be interpreted by specialised programs to represent a 3D image.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with PTSD. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. When multiple copies of reviews assessing the same topic were found, only the most recent and/or comprehensive was included. We prioritised reviews with pooled data for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[3-6].

- Moderate quality evidence found small to medium-sized reductions in total brain volume, intracranial volume, left insula, right insula, total insula, superior frontal gyrus, left middle temporal gyrus, inferior temporal gyrus, left anterior cingulate, total anterior cingulate, rostral anterior cingulate, lateral orbitofrontal cortex total amygdala, left hippocampus, right hippocampus, and total hippocampus in people with PTSD compared to controls.
- Moderate to low quality evidence found medium-sized effects of reduced hippocampus volume and large effects of reduced amygdala volume in people with PTSD who were exposed to childhood abuse compared to controls.
- Moderate quality evidence found small to medium-sized reductions in grey matter, cerebral volume, temporal lobe, hippocampus, and vermis in children with PTSD compared to controls. There were also non-significant, small reductions in the amygdala.

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- Moderate to low quality evidence found increased PTSD symptom severity was significantly associated with decreased volume of the left, but not the right, hippocampus.
- Compared to people with major depressive disorder, people with PTSD had reduced total brain volume and increased thalamus volume. Both PTSD and depression patients had significantly smaller hippocampal volume compared with controls, with no difference between the patient groups in this brain region.

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Ahmed-Leitao F, Spies G, van den Heuvel L, Seedat S

Hippocampal and amygdala volumes in adults with posttraumatic stress disorder secondary to childhood abuse or maltreatment: A systematic review

Psychiatry Research: Neuroimaging 2016; 256: 33-43

View review abstract online

Comparison	**Hippocampal and amygdala volumes in people with PTSD who were exposed to childhood maltreatment vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small samples, mostly inconsistent and imprecise, direct) found medium-sized effects of reduced hippocampus volume and large effects of reduced amygdala volume in people with PTSD who were exposed to childhood maltreatment compared to controls.**
Hippocampal and amygdala volumes	
Medium-sized effects showed reduced hippocampus volume in people with PTSD; Left hippocampus: 7 studies, N = 228, g = -0.66, 95%CI -0.93 to -0.39, $p < 0.00001$, I^2 = 0% Right hippocampus: 7 studies, N = 228, g = -0.77, 95%CI -1.26 to -0.29, p = 0.002, I^2 = 66% *Large effects showed reduced amygdala volume in people with PTSD;* Left amygdala: 4 studies, N = 131, g = -1.08, 95%CI -1.92 to -0.23, p = 0.013, I^2 = 79% Right amygdala: 4 studies, N = 131, g = -1.15, 95%CI -1.91 to -0.39, p = 0.003, I^2 = 73%	
Consistency in results‡	Consistent for left hippocampus only.
Precision in results§	Precise for left hippocampus only.
Directness of results‖	Direct

Bromis K, Calem M, Reinders A, Williams SCR, Kempton MJ

Meta-Analysis of 89 Structural MRI Studies in Posttraumatic Stress Disorder and Comparison With Major Depressive Disorder

American Journal of Psychiatry 2018; 175: 989-98

View review abstract online

Comparison	**Brain volume in people with PTSD vs. controls and vs. major**

	depression.
Summary of evidence	**Moderate quality evidence (medium to large sample, some inconsistency, precise, direct) found small to medium-sized reductions in total brain volume, intracranial volume, left insula, right insula, total insula, superior frontal gyrus, left middle temporal gyrus, inferior temporal gyrus, left anterior cingulate, total anterior cingulate, rostral anterior cingulate, lateral orbitofrontal cortex total amygdala, left hippocampus, right hippocampus, and total hippocampus.** **Compared to people with major depressive disorder, people with PTSD had reduced total brain volume and increased thalamus volume. Both PTSD and depression patients had significantly smaller hippocampal volume compared with control subjects, with no difference between the patient groups in this brain region.**
Brain volume	
Compared to controls, small to medium-sized effects showed reduced volume in people with PTSD; Total brain volume: 21 studies, N = 813, *g* = -0.27, 95%CI -0.41 to -0.13, *p* < 0.001, I^2 = 5% Intracranial volume: 13 studies, N = 472, *g* = -0.24, 95%CI -0.43 to -0.05, *p* = 0.012, I^2 = 10% Left insula: 3 studies, N = 125, *g* = -0.78, 95%CI -1.29 to -0.28, *p* = 0.002, I^2 = 43% Right insula: 3 studies, N = 125, *g* = -0.53, 95%CI -0.89 to -0.16, *p* = 0.005, I^2 = 0% Total insula: 5 studies, N = 324, *g* = -0.69, 95%CI -0.96 to -0.42, *p* < 0.001, I^2 = 23% Superior frontal gyrus: 4 studies, N = 266, *g* = -0.52, 95%CI -0.76 to -0.27, *p* < 0.001, I^2 = 0% Left middle temporal gyrus: 3 studies, N = 131, *g* = -0.38, 95%CI -0.74 to -0.02, *p* = 0.037, I^2 = 6% Inferior temporal gyrus: 3 studies, N = 166, *g* = -0.42, 95%CI -0.74 to -0.10, *p* = 0.009, I^2 = 4% Left anterior cingulate: 6 studies, N = 288, *g* = -0.40, 95%CI -0.69 to -0.11, *p* = 0.007, I^2 = 29% Total anterior cingulate: 9 studies, N = 505, *g* = -0.39, 95%CI -0.69 to -0.09, *p* = 0.010, I^2 = 60% Rostral anterior cingulate: 6 studies, N = 471, *g* = -0.35, 95%CI -0.58 to -0.13, *p* = 0.002, I^2 = 31% Lateral orbitofrontal cortex: 4 studies, N = 330, *g* = -0.57, 95%CI -0.96 to -0.18, *p* = 0.004, I^2 = 64% Total amygdala: 21 studies, N = 1,230, *g* = -0.26, 95%CI -0.51 to -0.01, *p* = 0.040, I^2 = 75% Left hippocampus: 38 studies, N = 1,641, *g* = -0.38, 95%CI -0.55 to -0.22, *p* < 0.001, I^2 = 58% Right hippocampus: 38 studies, N = 1,641, *g* = -0.42, 95%CI -0.59 to -0.26, *p* < 0.001, I^2 = 58 Total hippocampus: 41 studies, N = 1,900, *g* = -0.47, 95%CI -0.64 to -0.31, *p* < 0.001, I^2 = 62% In subgroup analysis of non-traumatised controls, people with PTSD had smaller total brain volume and volumes of grey matter, total, left, and right insula, total parahippocampal gyrus, and total, left, and right hippocampus. In subgroup analysis of traumatised controls, people with PTSD had smaller total brain volume,	

intracranial volume, superior frontal gyrus volume, total insula volume, anterior cingulate volume, lateral orbitofrontal cortex volume, and total and right hippocampal volume. Right and left parahippocampal gyri were significantly larger in the PTSD group compared with the traumatised controls. Compared with depressed patients, PTSD patients had significantly reduced total brain volume and increased thalamus volume. Both PTSD and depression patients had significantly smaller hippocampal volume compared with control subjects, with no difference between the patient groups in this brain region.	
Consistency in results	Some inconsistency.
Precision in results	Precise
Directness of results	Direct, apart from the comparison with major depression.

Kribakaran S, Danese A, Bromis K, Kempton MJ, Gee DG

Meta-analysis of Structural Magnetic Resonance Imaging Studies in Pediatric Posttraumatic Stress Disorder and Comparison With Related Conditions

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2020; 5: 23-34

View review abstract online

Comparison	**Brain volume in children with PTSD vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct) found small to medium-sized reductions in total grey matter, total cerebral volume, total, right, and left temporal lobe, total, right, and left hippocampus, and total vermis in children with PTSD compared to controls. There were also non-significant, small reductions in the total, left, and right amygdala in children with PTSD.**
Brain volume	
Small to medium-sized effects showed reduced volume in children with PTSD; Total grey matter: 3 studies, N = 328, g = -0.56, 95%CI -0.83 to -0.28, $p < 0.001$, $I^2 = 25\%$ Total cerebral volume: 3 studies, N = 328, g = -0.56, 95%CI -0.79 to -0.33, $p < 0.001$, $I^2 = 0\%$ Total temporal lobe: 4 studies, N = 265, g = -0.60, 95%CI -0.86 to -0.35, $p < 0.001$, $I^2 = 0\%$ Right temporal lobe: 3 studies, N = 247, g = -0.58, 95%CI -0.85 to -0.32, $p < 0.001$, $I^2 = 0\%$ Left temporal lobe: 3 studies, N = 247, g = -0.54, 95%CI -0.80 to -0.27, $p < 0.001$, $I^2 = 0\%$ Total hippocampus: 8 studies, N = 489, g = -0.51, 95%CI -0.88 to -0.13, $p = 0.007$, $I^2 = 73\%$	

Right hippocampus: 7 studies, N = 441, *g* = -0.51, 95%CI -0.93 to -0.09, *p* = 0.016, I^2 = 75% Left hippocampus: 7 studies, N = 441, *g* = -0.46, 95%CI -0.87 to -0.04, *p* = 0.030, I^2 = 75% Total vermis: 3 studies, N = 301, *g* = -0.46, 95%CI -0.88 to -0.04, *p* = 0.033, I^2 = 65% *There were small trend effects for reductions in the amygdala in children with PTSD;* Total amygdala: 8 studies, N = 504, *g* = -0.28, 95%CI -0.56 to 0.00, *p* = 0.052, I^2 = 54% Right amygdala: 8 studies, N = 504, *g* = -0.23, 95%CI -0.47 to 0.01, *p* = 0.060, I^2 = 40% Left amygdala: 8 studies, N = 504, *g* = -0.29, 95%CI -0.61 to 0.03, *p* = 0.073, I^2 = 44% There were no significant differences in the corpus callosum.

Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct

Nelson MD, Tumpap AM

Posttraumatic stress disorder symptom severity is associated with left hippocampal volume reduction: a meta-analytic study

CNS Spectrums 2017; 22: 363-72

View review abstract online

Comparison	**Association between PTSD symptom severity and hippocampal volume.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, direct) found increased PTSD symptom severity was significantly associated with decreased volume of the left, but not the right, hippocampus.**
Symptom severity and hippocampal volume	
Increased symptom severity was significantly associated with decreased volume of the left, but not the right, hippocampus; 19 studies, N = 297 Left hippocampus: β = -0.024, *p* < 0.004 Right hippocampus: β = -0.010, *p* < 0.21	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.

Directness of results	Direct

Explanation of acronyms

β = regression coefficient, CI = confidence interval, *g* = Hedges' g, standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[7].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[7].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[8]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[7];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[9].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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